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Review

Systematic review of pharmacologic and non-pharmacologic interventions to manage cognitive alterations after chemotherapy for breast cancer

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Abstract ***Purpose:*** Cognitive alterations are reported in breast cancer patients receiving chemotherapy. This has adverse effects on patients' quality of life and function. This systematic review investigates the effectiveness of pharmacologic and non-pharmacologic interventions to manage cognitive alterations associated with breast cancer treatment.
Methods: Medline via EBSCO host, CINAHL and Cochrane CENTRAL were searched for the period January 1999–May 2014 for prospective randomised controlled trials related to the management of chemotherapy-associated cognitive alterations. Included studies investigated the management of chemotherapy-associated cognitive alterations and used

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subjective or objective measures in patients with breast cancer during or after chemotherapy. Two authors independently extracted data and assessed the risk of bias.

Results: Thirteen studies involving 1138 participants were included. Overall, the risk of bias for the 13 studies was either high ($n = 11$) or unclear ($n = 2$). Pharmacologic interventions included psychostimulants ($n = 4$), epoetin alfa ($n = 1$) and Ginkgo biloba ($n = 1$). Non-pharmacologic interventions were cognitive training ($n = 5$) and physical activity ($n = 2$). Pharmacologic agents were ineffective except for self-reported cognitive function in an epoetin alfa study. Cognitive training interventions demonstrated benefits in self-reported cognitive function, memory, verbal function and language and orientation/attention. Physical activity interventions were effective in improving executive function and self-reported concentration.

Conclusion: Current evidence does not favour the pharmacologic management of cognitive alterations associated with breast cancer treatment. Cognitive training and physical activity interventions appear promising, but additional studies are required to establish their efficacy. Further research is needed to overcome methodological shortfalls such as heterogeneity in participant characteristics and non-standardised neuropsychological outcome measures.

1. Introduction

Alterations in cognitive function are often observed in patients receiving chemotherapy, particularly those treated for breast cancer [1]. These changes can comprise poor word or name recall, difficulty in staying focused, diminished ability to learn new things and a decreased ability to multitask [2]. Other alterations in executive function, information processing speed, language, motor function and spatial skills are documented. Depending on the nature of the malignancy and the treatment regimen, the time of onset, severity and duration of these changes are highly variable [3], as are its affective, functional and psychosocial outcomes [4].

Depending on the type of cancer investigated, estimates of the prevalence of cancer treatment-related alterations in cognitive function range from 16% to 75% during treatment [5], although they can endure beyond treatment. Supported by findings from neuropsychological tests, reports indicate that individuals can experience longer-term cognitive changes for as long as 21 years after chemotherapy for breast cancer [6]. In addition, imaging research has reported a correlation between deficits in cognitive function and white matter changes in the brain [7].

A number of systematic reviews and meta-analyses have investigated the prevalence of cognitive alteration and its association with treatment in cancer patients [2,8,9]. One systematic review [10] and one non-systematic narrative review, which discussed unpublished and ongoing studies [11], focused on interventions to enhance cognitive function. Both reviews, however, are limited in that they included non-randomised controlled trials. Furthermore, Hines et al. limited their studies to cognitive behavioural therapy (CBT), which does not encompass the full range of interventions available [10]. In summary, a high quality, comprehensive systematic review of interventions for managing chemotherapy-associated cognitive alterations is lacking.

This clinical problem has significant adverse effects on the post-treatment quality of life and function of patients with cancer; hence, interventions to prevent or manage it are warranted. Over the next decade, the number of individuals living with a cancer diagnosis is projected to increase by 31%, with a high proportion being patients with breast cancer [12]. Treatment-associated adverse effects in this growing population have significant public health implications if they are not well managed. In this paper, we systematically review the effectiveness of pharmacologic and non-pharmacologic interventions to manage alterations of cognitive function associated with breast cancer treatment.

2. Method

This systematic review adhered to the PRISMA statement [13] for reporting systematic reviews.

2.1. Search strategy

A medical librarian (JD) searched Medline via EBSCOhost, CINAHL and Cochrane CENTRAL for studies published between January 1999 and May 2014. The key search terms were chemotherapy, antineoplastic agents, chemoradiotherapy, cancer, neoplasms, randomised controlled trial, cognitive impairment, cognitive dysfunction, cognitive disorder, cognitive loss, cognitive deficit and memory disorder. The search was limited to prospective randomised controlled trials (RCTs) published in English that investigated the management of chemotherapy-associated cognitive alterations (as primary or secondary outcomes). Further manual searches of the reference lists of the relevant studies and reviews were undertaken by authors AC, RC and AM.

2.2. Study selection

Three authors (RC, AM and AC) pre-screened all the search results (titles and abstracts) and after consensus was reached for possible inclusion, the full text of all selected papers was assessed. Studies were included if they were prospective RCTs; reported pharmacologic or non-pharmacologic interventions for cognitive alterations in breast cancer patients during or after chemotherapy or multimodal therapy including chemotherapy; and used subjective or objective measures of cognitive function. Investigations of patients with secondary brain metastases and studies with less than 50% of breast cancer patients in the sample or with patients receiving radiation monotherapy were excluded. Unpublished reports, letters to the editor, retrospective chart reviews and non-RCTs were also excluded.

2.3. Data extraction and rating of articles for risk of bias

Two authors (RC, AM or AC) independently extracted the data using a pre-designed, piloted form. Studies were independently rated according to the Cochrane Collaboration's risk of bias (ROB) criteria for a high, low or unclear ROB with respect to random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias [14]. An 'unclear' ROB was assigned to a study if the risk was unclear in one or more domains, with no domain rated as high risk. A 'high' ROB was assigned to a study if the risk was high in one or more domains. A 'low' ROB was assigned to a study rated as low risk in all domains [15]. Differences in ratings were settled by discussion or by a third person if consensus was not achieved by the two primary reviewers.

Studies that compared an intervention to usual care, placebo or another intervention and that presented adequate data for the calculation of effect size were evaluated. To determine the effects of the interventions in any of the included studies, effect sizes (mean difference [MD] or relative risk with a 95% confidence interval [CI]) were calculated using Review Manager 5 [14]. We classified outcome assessments of <3 months, 3–6 months and $\geqslant 6$ months as short-, medium- and long-term time points, respectively. If more than one measurement was reported within the defined period, the latest assessment was extracted. When published articles presented insufficient data to calculate the effect sizes, the authors were contacted for the required information. Although some studies reported statistical analyses for within-group changes from the baseline, between-group differences were analysed to determine the effects of the interventions (positive, negative or inconclusive). Data elicited from screening measures (e.g. Mini Mental Status Exam or High Sensitivity Cognitive Screen) were not extracted or analysed. Objective outcome data were classified into the seven pre-defined domains of cognitive function recommended by Lezek et al. [16] and Hodgson et al. [17].

The interventions and outcome measurements reported in these studies were heterogeneous. Therefore, meta-analysis was not undertaken.

3. Results

Screening of 555 citations identified a total of 29 potentially relevant papers, the full texts of which were retrieved. Thirteen of the 29 studies were excluded as the majority of the included participants did not have breast cancer [18–30]; two studies did not include cognitive function measurement [31,32]; and one study was not an RCT [33]. Thirteen studies met the inclusion criteria for quantitative and qualitative analyses. A flowchart detailing the identification of studies is provided in Fig. 1.

Thirteen studies with a total of 1138 participants were included in this review [34–46]. Eleven were undertaken in North America, one in Japan and the other in France. Six studies evaluated pharmacologic interventions (psychostimulants, $n = 4$; erythropoietin stimulating agent, $n = 1$, Gingko biloba, $n = 1$). Seven studies investigated non-pharmacologic interventions, five of which involved cognitive training through forms of cognitive behavioural ($n = 4$) or mindfulness therapy ($n = 1$) and two of which explored physical activity. The characteristics of the included studies, the age of participants, treatments received, time since chemotherapy, sample sizes, assessment outcomes and time points for assessments are listed in Table 1.

Ten studies provided specific information on how the random sequence was generated. One provided sufficient information on allocation concealment [38]. The blinding of participants, personnel and outcome assessments was achieved in the six pharmacologic placebo trials but was not possible in the seven non-pharmacologic interventions. The risk of incomplete data outcome reporting bias was detected in six trials [34–37,44,45], which did not provide reasons for participant dropout, or did not undertake intention-to-treat analyses. Three studies [35,37,38] had selective outcome reporting bias, as they did not report the data on all outcomes measured. Overall, the ROB for the 13 studies was either high [34–40,43–46] ($n = 11$) or unclear [41,42] ($n = 2$) (Table 2).

3.1. Pharmacologic interventions

3.1.1. Psychostimulants

Psychostimulants including d-methylphenidate (d-MPH) ($n = 2$), methylphenidate ($n = 1$) and modafinil ($n = 1$) were evaluated. Two studies [41,42] evaluated

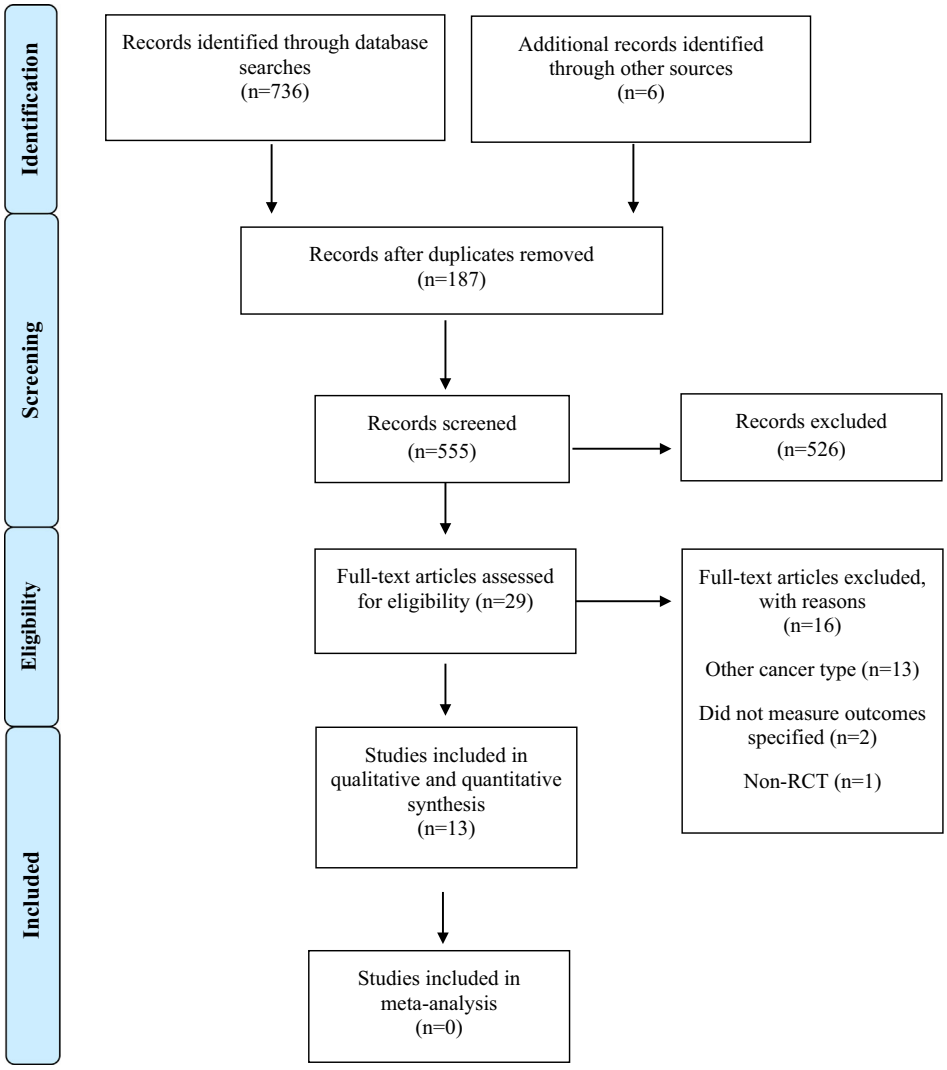

Fig. 1. PRISMA flow diagram.

the effects of d-MPH on cognitive function. In Lower et al.'s study [41], patients were prescribed on 5 mg d-MPH twice daily with doses titrated weekly to a maximum of 50 mg/day over 8 weeks. In the other d-MPH study, conducted by Mar Fan et al. [42] patients who demonstrated compliance through a placebo run-in phase were randomised to d-MPH 5 mg twice daily or to matched placebo. Doses were titrated to a maximum of 10 mg twice daily until the end of the final cycle of chemotherapy. In another cross-over study [37], breast cancer patients were randomised to methylphenidate 18 mg/day for 2 weeks followed by placebo for 2 weeks or vice versa. Modafinil was trialed in a study involving two phases [40]. In the first phase, all patients received modafinil 100 mg once daily for 3 days and 200 mg once daily during an open-label period of 4 weeks. In the subsequent phase, patients who achieved a positive response in terms of attention and memory in the first phase were randomised to an additional 4 weeks of modafinil 200 mg/day or placebo. In the assessment of short-term and medium-term cognitive measures between the psychostimulants and controls, there was no statistically significant difference in cognitive measures in any of the studies (Table 3).

3.1.2. Epoetin alfa (EPO)

O'Shaughnessy et al. [45] evaluated whether epoetin alfa (EPO) could enhance cognitive and execution function in patients with breast cancer receiving adjuvant chemotherapy. Patients were randomised to receive 40,000 U of EPO subcutaneously weekly or a comparable volume of placebo during adjuvant or neoadjuvant chemotherapy over a maximum of 12 weeks. EPO doses were titrated according to haemoglobin levels. An improvement in self-perceived cognitive function (EXIT-25) was noted in patients receiving EPO compared to a placebo (MD = −1.60 [95% CI, −2.81 to −0.39]).

3.1.3. Gingko biloba

Barton et al. [34] investigated whether Ginkgo biloba could prevent cognitive impairment in breast cancer

Table 1
Characteristics of included studies ($n = 13$).

Study	Participants	Prior treatments	Time since chemotherapy	Comparisons	Domains examined	Assessed time point
Barton (2013) [34] USA	Breast CA: Both arms: 100% Age: I : ⩾50 years: 50% C: ⩾50 years: 50%	I: AC: 33%; AC and taxane: 52% Others: 15% Tam planned: 51% C: AC: 36%; AC and taxane: 52% Others: 12% Tam planned: 54%	During chemo	Ginkgo biloba 60 mg versus placebo twice daily (started at the second cycle of chemo and ceased at 1 month after completion of chemo) I: $n = 107$ C: $n = 103$	Orientation and attention, self-reported cognitive function	Short-term, medium-term, long-term
Culos-Reed (2006) [35] Canada	Breast CA: Both arms: 100% Age: Both arms: 51.2 (10.3)	Both arms: Chemo: percentage not stated	>3 months post chemo	7-week yoga programme versus control I: $n = 10$ C: $n = 10$	Self-reported cognitive function	Short-term
Dolbeault (2009) [36] France	Breast CA: Both arms: 100% Age: I: 54.5 (9.3) C: 51.6 (9.6)	I: Chemo: 45.1% C: Chemo: 61.4%	Not stated	A CBT-based psycho-educational group intervention (8 weekly 2-h sessions) versus control (usual care) I: $n = 102$ C: $n = 101$	Self-reported cognitive function	Short-term
Escalante (2014) [37] USA	Breast CA: Both arms: 100% Age: Both arms: Median 57 (Range: 32–79)	Both groups: Chemo: 100%	Either undergoing or completed treatment in the previous 12 months	Methylphenidate (18 mg daily) versus placebo for 14 days $n = 42$ (cross-over design)	Orientation and attention	Short-term
Ferguson (2012) [38] USA	Breast CA: Both arms: 100% Age: I: 51.2 (7.3) C: 49.4 (5.1)	I: Received AC/FAC C: Received AC/FAC	>18 months post chemo	8-week Memory and Attention Adaptive Training (MAAT) versus waitlist control I: $n = 19$ C: $n = 21$	Orientation and attention, executive function and motor function, memory, self-reported cognitive function	Short-term
Kesler (2013) [39] USA	Breast CA: Both arms: 100% Age: I: 55.0 (7) C: 56.0 (6)	I: 100% chemo 70% RT 60% HT C: 100% chemo 63% RT 63% HT	Mean (SD): 6.0 (3) months	Online computerised training programme (5 exercises 4 times weekly for 12 weeks) versus usual care I: $n = 21$ C: $n = 21$	Orientation and attention, executing functioning and motor function, verbal function and language skills, memory, self-reported cognitive function	Short-term
Kohli (2012) [40] USA	Breast CA: Both arms: 100% Age: I: 54.0 (10.3) C: 56.35 (11.4)	I: 100% chemo, 82% RT C: 100% chemo, 85% RT	>30 days post chemo	Modafinil 200 mg daily versus placebo for 4 weeks I: $n = 34$ C: $n = 34$	Orientation and attention, memory	Short-term

(*continued on next page*)

Table 1 (*continued*)

Study	Participants	Prior treatments	Time since chemotherapy	Comparisons	Domains examined	Assessed time point
Lower (2009) [41] USA	Breast CA: I: 78% C: 73% Age: I: 52.5 (10.2) C: 53.2 (8.4)	I: 100% chemo C: 100% chemo	Mean (SD): 115.3 (106.5) weeks	D-methylphenidate versus placebo for 8 weeks; dose modifications were allowed; max 50 mg/day I: $n = 76$ C: $n = 78$	Orientation and attention	Short-term
Mar Fan (2008) [42] Canada	Breast CA: Both arms: 100% Age: I: Median = 50, Range = 36–72 C: Median = 51, Range = 37–74	Both arms: 100% Chemo Both arms: AC: 100% Cy: 96.5% 5FU: 33.3% Taxane: 31.6%	I: Median (range): 84 (23–141) days post chemo C: Median (range): 85 (26–131) days post chemo	D-methylphenidate (titration: 5to 10 mg twice daily) versus placebo until final cycle of chemo I: $n = 28$ C: $n = 29$	Memory	Short-term
Miki (2014) [43] Japan	Breast CA: I: 55.3% C: 55.0% Age: I: 72.97 (4.57) C: 75.45 (6.57)	I: 81.6% Surgery 23.7% Chemo 68.4% HT 68.4% RT C: 72.5% Surgery 27.5% Chemo 80.0% HT 4.00% RT	Not stated	4-week Speed-feedback therapy with a bicycle ergometer versus usual care I: $n = 38$ C: $n = 40$	Executing function and motor function	Short-term
Milbury (2014) [44] USA	Breast CA: Both arms: 100% Age: I: 53.0 (6.6) C: 54.1 (8.6)	I: 100% chemo 73.9% RT 87% Surgery C: 100% chemo 79.2% RT 100% Surgery	6–60 months post chemo	Tibetan sound meditation (2x weekly sessions for 6 weeks) versus waitlist control I: $n = 18$ C: $n = 24$	Orientation and attention, memory, verbal functions and language skills, self-reported cognitive function	Short-term
O'Shaughnessy (2005) [45] USA	Breast CA: Both arms: 100% Age: I: 53.3 (9.7) C: 54.3 (12)	Both arms: 100% chemo Both arms: Doxorubicin/eprubicin:100% Cy: 96.8% 5-FU: 11.7% Taxane: 24.5%	Undergoing chemo	40,000U epoetin alfa subcutaneous weekly versus placebo (started on D1 of cycle 1 of 4 cycles of chemo, and continued for a maximum of 12 weeks) I: $n = 47$ C: $n = 47$	Executive function and motor function, self-reported cognitive function	Short-term, long-term
Von Ah (2012) [46] USA	Breast CA: All three arms: 100% Age: I1: 55.19 (7.58) I2: 56.93 (7.83) C: 57.21 (9.8)	All three arms: 100% chemo	1 year post chemo	Memory training (Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) programme (10 sessions for 6–8 weeks) versus speed of processing training (Posit Science®) (10 sessions for 6–8 weeks) versus waitlist group I1: $n = 29$ I2: $n = 30$ C: $n = 29$	Memory, self-reported cognitive function	Short-term

Abbreviations: 5-FU: 5-Fluorouracil; AC: Anthracycline and cyclophosphamide; C: Control; CBT: Cognitive behavioural therapy; Cy: Cyclophosphamide; Chemo: Chemotherapy; FAC: 5-Fluorouracil, anthracycline and cyclophosphamide; HT: Hormonal therapy, I: Intervention, RT: Radiation therapy. Tam: Tamoxifen. Measurement time points: short term: less than 3 months; medium term: 3–6 months; long term: beyond 6 months.

Table 2
Risk of bias (ROB) table for included studies ($n = 13$).

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Level of risk
Barton (2013) [34]	+	0	+	+	–	+	+	H
Culos-Reed (2006) [35]	0	0	0	–	–	–	+	H
Dolbeault (2009) [36]	+	0	–	–	–	+	+	H
Escalante (2014) [37]	0	0	+	+	0	–	+	H
Ferguson (2012) [38]	+	+	+	+	+	–	+	H
Kesler (2013) [39]	+	0	–	0	+	+	+	H
Kohli (2012) [40]	+	0	+	+	+	+	–	H
Lower (2009) [41]	+	0	+	+	+	+	+	U
Mar Fan (2008) [42]	0	0	+	+	+	+	+	U
Miki (2014) [43]	+	0	–	+	+	+	+	H
Milbury (2014) [44]	+	0	–	0	0	+	+	H
O'Shaughnessy (2005) [45]	+	0	+	+	–	+	+	H
Von Ah (2012) [46]	+	0	–	–	+	+	+	H

0 represents an unclear ROB; – represents a high ROB and + represents a low ROB. *Abbreviations:* H, high ROB (–) for one or more domains; L, low ROB (+) for all domains; U, unclear ROB for one or more domains.

patients receiving adjuvant chemotherapy. Patients were randomised to receive Ginkgo biloba 60 mg twice daily or a placebo. The intervention commenced at the second cycle of chemotherapy and continued until 1 month after the completion of chemotherapy. The authors concluded that there were no significant differences in either subjective or objective cognitive measures between the two groups.

3.1.4. Toxicities of pharmacologic interventions

Five of the six studies [34,37,41,42,45] evaluating pharmacologic interventions reported adverse events associated with the interventions and the placebo. The adverse events were generally mild, with few Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 toxicities were reported. In the two studies investigating d-MPH versus a placebo [41,42], higher incidences of dry mouth, nausea, dizziness, insomnia, anxiety and nervousness were reported among patients receiving d-MPH compared to the placebo. Similar findings were found in the methylphenidate study [37]. In the EPO study, O'Shaughnessy et al. [45] reported a fatal cerebrovascular accident in one patient in the EPO group. Gingko biloba was generally well tolerated compared to the placebo, with the exception of nausea, which was worse in the placebo group [34].

3.2. Non-pharmacologic interventions

3.2.1. Cognitive training

In their three-arm study, Von Ah et al. [46] delivered memory training in one arm and speed processing training in the other. Memory training entailed the teaching of strategies to remember word lists, sequences and text material and learning how to apply the principles of meaningfulness, organisation, visualisation and association to these activities. Strategies focused on multiple mnemonic techniques. The intervention comprised 10 sessions, the first five comprising strategy instruction and practice, and the last five comprising practical exercises. This study reported a significant improvement in memory using objective neuropsychological testing compared to the control group, measured using composite scores for both immediate memory recall (MD = 0.31, [95% CI, 0.04–0.58]) and long term delayed memory (MD = 0.46, [95% CI, 0.12–0.80]). When self-perceived cognition for this intervention was measured with the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog), the results demonstrated a statistically significant improvement in the intervention group compared to the control group (MD = 9.85 [95% CI, 1.67–18.03]) (Table 4). The other arm of the study involved speed processing training, which aimed to systematically reduce stimulus duration during a series of progressively more difficult computerised information processing tasks. Exercises comprised time-order judgment, discrimination, spatial match, forward span, instruction following and narrative memory tasks. Although the speed processing training did not target specifically at memory improvement, the training yielded positive improvement in memory, measured using composite scores for both immediate memory recall (MD = 0.43, [95% CI, 0.16–0.70]) and long term delayed memory (MD = 0.47, [95% CI, 0.13–0.81]).

Kesler et al. [39] targeted executive function, which in their study encompassed working memory, cognitive flexibility, multitasking, planning and attention. The intervention comprised an online computerised training programme undertaken in the participants' homes. It spanned 48 sessions of 20–30 min each over 6 weeks, with each session comprising combinations of 13 different exercises to enhance core executive function. Each participant logged in four times per week to complete five separate exercises. Exercises involved computerised visual stimuli that required a motor response such as a mouse click plus immediate feedback and reinforcement.

Table 3
Pharmacologic interventions and outcomes ($n = 6$).

Categories	Intervention	Tool	Domains examined	Assessment time point	Effect size	Conclusion
Psychostimulants	Dexmethylphenidate [41]	Modified Swanson, Nelson and Pelham Attention Deficit/ Hyperactivity Scale (SNAP)	Orientation and attention	Short-term	MD = 0.30 (95% CI, −2.19 to 2.79)	Negative
	Dexmethylphenidate [42]	Hopkins Verbal Learning Test-Revised (HVLT-R)	Memory	Medium-term	RR = 1.20 (95% CI, 0.72–2.00)	Negative
	Methylphenidate [37]	Digit Span	Orientation and attention	Short-term	Data not reported	Inconclusive
	Modafinil [40]	Cognitive Drug Research Computerised Assessment System[#] (Power of Attention)	Orientation and attention	Short-term	MD = −27.64 (95% CI, −89.66 to 34.38)	Negative
		Cognitive Drug Research Computerised Assessment System[#] (Continuity of Attention)	Orientation and attention	Short-term	MD = 0.65 (95% CI, −0.65 to 1.95)	Negative
		Cognitive Drug Research Computerised Assessment System[#] (Episodic Secondary Memory)	Memory	Short-term	MD = −4.52 (95% CI, −29.84 to 20.80)	Negative
		Cognitive Drug Research Computerised Assessment System[#] (Working Memory)	Orientation and attention	Short-term	MD = 0.12 (95% CI, −0.06 to 0.30)	Negative
		Cognitive Drug Research Computerised Assessment System[#] (Speed of Memory)	Orientation and attention	Short-term	MD = −103.46 (95% CI, −567.03 to 360.10)	Negative
Erythropoietic stimulating agent	Epoetin alfa [45]	Executive Clock Drawing Task 1 (CLOX1)	Executive function and motor function	Short-term	MD = 0.10 (95% CI, −0.93 to 1.13)	Negative
		Executive Clock Drawing Task 1 (CLOX1)	Executive function and motor function	Long-term	MD = −0.80 (95% CI, −1.83 to 0.23)	Negative
		The Executive Interview (EXIT-25)	Self-reported cognitive function	Short-term	MD = −1.60 (95% CI, −2.81 to −0.39)[*]	Positive
		The Executive Interview (EXIT-25)	Self-reported cognitive function	Long-term	MD = −0.10 (95% CI, −1.35 to 1.15)	Negative
Complementary alternative medicine	Gingko biloba [34]	Trail Making Test-A	Orientation and attention	Short-term, medium-term, long-term	Data not extractable	Inconclusive
		Trail Making Test-B	Orientation and attention	Short-term, medium-term, long-term	Data not extractable	Inconclusive

Positive represents 'favours intervention' and Negative represents 'does not favour intervention'. Measurement time points: short-term: less than 3 months; medium-term: 3–6 months; long-term: beyond 6 months. *Abbreviations:* MD, mean difference; CI, confidence interval.
[*] $p < 0.05$.
[#] These subtest names do not appear in the original paper–they are derivative measures of a factor analysis.

The exercises were adaptive to individual activity, with the level of difficulty and complexity increasing according to a pre-determined algorithm. Compared to controls, the intervention participants demonstrated statistically significant improvements in executive function as measured by the Delis–Kaplan measure of verbal function and language skills (MD = 2.00 [95% CI, 0.78–3.22]) and the Symbol Search measure of orientation and attention (MD = 2.00 [95% CI, 0.16–3.84]).

Dolbeault et al. [36] delivered a CBT-based stress management intervention in which cognition, a secondary objective, was measured with the European Organisation for Research and Treatment of Cancer (EORTC)-Cognitive Functioning subscale. Results were not statistically significant for enhancements in cognitive function. In another study, rather than traditional repetitive techniques of mental exercise in CBT that aim to repair damaged neuro-circuitry to recover memory

Table 4
Non-pharmacologic interventions and outcomes ($n = 7$).

Categories	Intervention	Tool	Domains examined	Assessment time point	Effect size	Conclusion
Cognitive training	Computerised cognitive training [39]	Wisconsin card sorting test	Executive function and motor function	Short-term	MD = 3.00 (95% CI, −1.49 to 7.49)	Negative
		Delis–kaplan (letter fluency)	Verbal function and language skills	Short-term	MD = 2.00 (95% CI, 0.78 to 3.22)*	Positive
		Digit span	Orientation and attention	Short-term	MD = 0.90 (95% CI, −3.17 to 1.17)	Negative
		Symbol search	Orientation and attention	Short-term	MD = 2.00 (95% CI, 0.16 to 3.84)*	Positive
		Hopkins verbal learning test-revised (HVLT-R)	Memory	Short-term	MD = 1.00 (95% CI, −5.95 to 3.95)	Negative
		BRIEF GEC	Self-reported cognitive function	Short-term	MD = −2.00 (95% CI, −10.37 to 6.37)	Negative
		BRIEF GEC (plan and organise)	Self-reported cognitive function	Short-term	MD = −5.00 (95% CI, −13.30 to 3.30)	Negative
		BRIEF GEC (task monitor)	Self-reported cognitive function	Short-term	MD = −4.00 (95% CI, −10.75 to 2.75)	Negative
	Cognitive-behavioural therapy [38]	Trail Making Test-B	Orientation and attention	Short-term	MD = 3.22 (95% CI, −7.9 to 14.34)	Negative
		Colour word trail (D-KEFS subset)	Executive function and motor function	Short-term	MD = −0.73 (95% CI, −6.44 to 4.98)	Negative
		Colour word switching trail (D-KEFS subset)	Executive function and motor function	Short-term	MD = 0.53 (95% CI, −6.81 to 7.87)	Negative
		Digit symbol-coding (subtest of wechsler adult intelligence scale)	Orientation and attention	Short-term	MD = 1.09 (95% CI, −0.75 to 2.93)	Negative
		California verbal learning test (CVLT) ii	Memory	Short-term	MD = 4.26 (95% CI, −2.32 to 10.84)	Negative
		MASQ scores	Self-reported cognitive function	Short-term	MD = 4.02 (95% CI, −8.83 to 16.87)	Negative
	Memory training [46]	FACT-Cog	Self-reported cognitive function	Short-term	MD = 9.85 (95% CI, 1.67–18.03)*	Positive
		Composite score: rey auditory verbal learning test (AVLT) (sum recall, short delay and recognition score and rivermead behavioral paragraph recall test (immediate recall score)	Memory	Short-term	MD = 0.31 (95% CI 0.04–0.58)*	Positive
		Composite score: rey auditory verbal learning test (AVLT) (long term delay score) and rivermead behavioural paragraph recall test (long term delay score)	Memory	Short-term	MD = 0.46 (95% CI, 0.12−0.80)*	Positive
	Speed of processing training [46]	FACT-Cog	Self-reported cognitive function	Short-term	MD = 6.66 (95% CI, −1.43 to 14.75)	Negative
		Composite score: rey auditory verbal learning test (AVLT) (sum recall, short delay and recognition score and rivermead behavioral paragraph recall test (immediate recall score)	Memory	Short-term	MD = 0.43 (95% CI, 0.16−0.70)*	Positive
		Composite score: rey auditory verbal learning test (AVLT) (long term delay score) and rivermead behavioral paragraph recall test (long term delay score)	Memory	Short-term	MD = 0.47 (95% CI, 0.13–0.81)*	Positive

(*continued on next page*)

Table 4 (*continued*)

Categories	Intervention	Tool	Domains examined	Assessment time point	Effect size	Conclusion
	Psycho-education [36]	EORTC-CF	Self-reported cognitive function	Short-term	MD = −0.16 (95% CI, −0.38 to 0.06)	Negative
	Tibetan sound [44]	Rey auditory verbal learning test (AVLT)	Memory	Short-term	Data not extractable	Inconclusive
		Digit span	Orientation and attention	Short-term	MD = 0.43 (95% CI, −0.17 to 1.03)	Negative
		Digit symbol-coding (subtest of wechsler adult intelligence scale)	Orientation and attention	Short-term	MD = 0.46 (95% CI, −0.14 to 1.06)	Negative
		Controlled oral word association test	Verbal function and language skills	Short-term	MD = 0.00 (95% CI, −0.66 to 0.66)	Negative
		FACT-Cog (impairment)	Self-reported cognitive function	Short-term	MD = 3.70 (95% CI, −8.20 to 15.60)	Negative
		FACT-Cog (ability)	Self-reported cognitive function	Short-term	MD = 1.40 (95% CI, −3.06 to 5.86)	Negative
		FACT-Cog (other comment)	Self-reported cognitive function	Short-term	MD = 0.40 (95% CI, −1.57 to 2.37)	Negative
		FACT-Cog (impact)	Self-reported cognitive function	Short-term	MD = 0.10 (95% CI, −4.28 to 4.48)	Negative
Exercise	Speed-feedback therapy with a bicycle ergometer [43]	Frontal assessment battery	Executive function and motor function	Short-term	MD = 1.66 (95% CI, 0.84–2.48)*	Positive
	Yoga [35]	Symptoms of stress inventory (SOSI) cognition subscale	Self-reported cognitive function	Short-term	MD = −1.67 (95% CI, −3.66 to 0.32)	Negative
		Profile of moods scale (POMS) concentration subscale	Self-reported cognitive function	Short-term	MD = −2.50 (95% CI, −4.56 to −0.44)*	Positive

Positive represents 'favours intervention' and Negative represents 'does not favour intervention'. *Abbreviations:* BRIEF GEC: Behaviour Rating Inventory of Executive Function Global Executive Composite; EORTC-CF: European Organisation for Research and Treatment of Cancer-Cognitive functioning subscale; FACT-Cog: Functional Assessment of Cancer Therapy-Cognitive Function; GEC: Global Executive Composite; MASQ: Multiple Abilities Self-Report Questionnaire; CI: confidence interval; MD: mean difference. Measurement time point: short-term: less than 3 months.

* $p < 0.05$.

function, Ferguson et al. [38] taught strategies for cognitive processing and new behaviour that compensated for chronic memory dysfunction. This intervention entailed the participants monitoring their cognitive failures and learning new processes to succeed in daily activities in which memory was required. The participants undertook twice weekly face-to-face sessions of 30–50 min each, with reinforcing phone contacts between each visit. Differences in all outcome measures between intervention and control were not significant.

Milbury et al. [44] delivered a Tibetan sound meditation intervention, based on the premise that the focused concentration of such meditation, coupled with awareness, stress reduction and relaxation techniques would improve objective cognitive performance. Each participant undertook 60-min meditation classes twice weekly for 6 weeks. Compared to controls, the intervention did not result in significant differences in objectively or subjectively measured cognitive function.

3.2.2. Physical activity

One physical activity intervention [43] comprised speed feedback therapy with a bicycle ergometer connected to a computer. Participants pedaled the bike to match the target arbitrarily displayed on the computer screen, which appeared as a pathway. The participants were instructed to pedal while visually tracking the path, and they undertook one pedaling session per week for 4 weeks. The exercise load was pre-set, with the participants pedaling for 5 min each session. Compared to controls, the intervention participants had improved executive function and motor function as measured by the Frontal Assessment Battery (MD = −2.50 [95% CI, −4.56 to −0.44]).

Culos-Reed et al. [35] delivered a programme of modified hatha yoga, which focused on relaxation and awareness of breathing, body sensations and thoughts, to enhance post-treatment quality of life. Participants progressively built flexibility, strength and balance while maintaining awareness and relaxation. A reduction of cognitive disorganisation (as measured by the Profile of Mood State [POMS] Concentration subscale) was demonstrated in the intervention group compared to the control immediately on conclusion of the programme (MD = −2.50 [95% CI, −4.56 to −0.44]).

4. Discussion

Current evidence does not favour the pharmacologic management of cognitive alteration associated with breast cancer treatment. The inherent variability of the psychology-derived cognitive training interventions makes it difficult to determine their role in practice. Some forms of cognitive training, particularly those that focus on quality of life enhancements, hold potential. For example, one study demonstrated a clinically important (i.e. subjectively reported) and statistically significant benefit in cognition-related quality of life [46]. Physical activity interventions also appear promising; however, methodological challenges in these studies preclude any concrete recommendations for practice.

Psychostimulants effectively manage cognitive issues related to attention deficit hyperactivity disorder and neurodegenerative diseases. The studies included in this review hypothesised that these agents are as effective in treating chemotherapy-associated cognitive alterations. These drugs include methylphenidate and d-MPH, which are sympathomimetic amines that modulate neurotransmitters in the brain. They are short-acting and were prescribed for a limited time during chemotherapy in these studies; therefore, the long-term benefits were not assessed. The long-term benefits of psychostimulants have not been established [47], which suggests limited clinical benefits for individuals previously treated for breast cancer [37,41,42]. Similar to the sympathomimetics, modafinil improves wakefulness by acting on specific pathways in the brain that regulate sleep-wake patterns, without increasing the risk of the extrapyramidal side-effects that are commonly observed with sympathomimetics. Although patients receiving this treatment achieved a level of improvement in the open-label phase of the study [40], this review did not detect any subsequent benefit in the randomised phase. In summary, the role of these agents is limited. In addition to conventional medications, herbal supplements such as Ginkgo biloba were also investigated as potential cognitive enhancers [34]. The literature indicates that Ginkgo biloba may improve cognitive function in patients with mild or moderate Alzheimer's disease or dementia [48,49]. However, no benefits were observed in the study by Barton et al. [34]. The authors proposed that the mechanisms underpinning chemotherapy-induced cognitive changes are different from those associated with dementia [34].

In terms of non-pharmacologic interventions, cognitive training is useful in a range of conditions such as traumatic brain injury, which, like chemotherapy-associated dysfunction, demonstrate more subtle cognitive impairment [39]. Physical activity and cognitive training techniques involve repeated skills and awareness practice, adaptive difficulty levels and an engaging and rewarding environment. It is possible that these aspects of the interventions might not necessarily target cognitive function. However, they could yield positive benefits in cognitive organisation due to overall enhancement of self-reported quality of life [38]. Given that quality of life was a primary or secondary end-point in six of the seven non-pharmacologic studies in this review, and that improvements in the participants' quality of life were integral to many of these interventions, this assumption is worthy of empirical investigation.

A number of other interventions not included in this review also warrant further exploration. For example,

the effectiveness of cholinesterase inhibitors (such as donepezil) and antioxidants (such as vitamin E) were investigated in the prevention of cognitive decline in patients with small cell lung cancer [50]. Unfortunately, poor patient accrual led to the early closure of the study. The results of trials of granulocyte macrophage-colony stimulating factor [50], memantine [19] and medical qigong [29] are also promising, and further evaluations are required.

A number of methodological limitations featured in the included studies. First, there was at least one ROB in all of the studies. Second, the treatment characteristics of the participants were variable (e.g. they were at different stages of the disease, or received different treatment regimens). Third, the studies did not explain whether the participants were primed for cognitive impairment, with the entry criteria of many studies stipulating self-reported cognitive function. Fourth, the participants could not be blinded to the intervention in the non-pharmacologic studies. Fifth, many interventions required an intense commitment and repeat visits from participants, yet their sustainability over time is hard to determine, particularly where losses to follow-up were not documented [34–37,44,45]. Eleven studies did not evaluate the sustainability of effects beyond 3 months, by which time most of the interventions had ceased. Sixth, the majority of studies involved less than 50 participants per arm, although we recognize that many were pilot and feasibility investigations, which are integral components of high-quality research programmes. We also recognize that there may be a potential risk of publication bias with studies reporting negative results remaining unpublished.

Seventh, some of the included studies did not include cognitive function as a primary end-point. Trials are often not powered to detect differences in secondary outcomes. However, we included these studies due to the potential for meta-analysis. Finally, the majority of the studies were undertaken in North America. Given that a patient's symptom experience is often culturally specific [51], the generalisability of these results to other sociocultural contexts is uncertain.

The problems reflected in the range of methodologies and different cognitive outcomes reported in these studies could be addressed through the harmonisation of intervention studies. The International Cognition and Cancer Task Force [52] provide some useful guidance in this respect. They recommend for observational studies that pre-treatment cognitive function is assessed, that intervention and control groups are standardised in terms of regimen and type of cancer, and that neuropsychological outcome measures are harmonised. These principles are equally germane to intervention studies.

This review suggests that in any intervention study in this field, the patient cohort requires careful consideration in terms of the stage of cancer and time since diagnosis. Studies could incorporate a screen for expectancy effects prior to randomisation that are controlled for during data analysis. Expectancies and stereotypes including those associated with diagnoses are known to influence cognitive profiles [53]. Screening should also assess premorbid cognitive function if possible [54]. Subjective and objective measurements appear to be equally important in detecting effects. Self-reported measures detect outcomes that are clinically significant to patients, whereas objective neuropsychological tests remain the gold standard [52]. Utilisation of validated tools would also be essential for future interventional studies.

Future studies would benefit from the addition of an attention control arm to address the bias inherent in the inability to blind in non-pharmacologic studies [55,56]. The potential uptake of the intervention should also be carefully considered. Aside from feasibility studies to determine this, interventions need to be accessible and easy for patients to undertake. Technology-enhanced interventions have promise, particularly multimodal programmes that combine physical activity and cognitive training.

In summary, the burden associated with this commonly reported problem in the breast cancer community is significant. The science to address this problem, however, is imprecise. Well-designed clinical studies are clearly warranted to enhance the quality of life and function of this growing population.

Conflict of interest statement

None declared.

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